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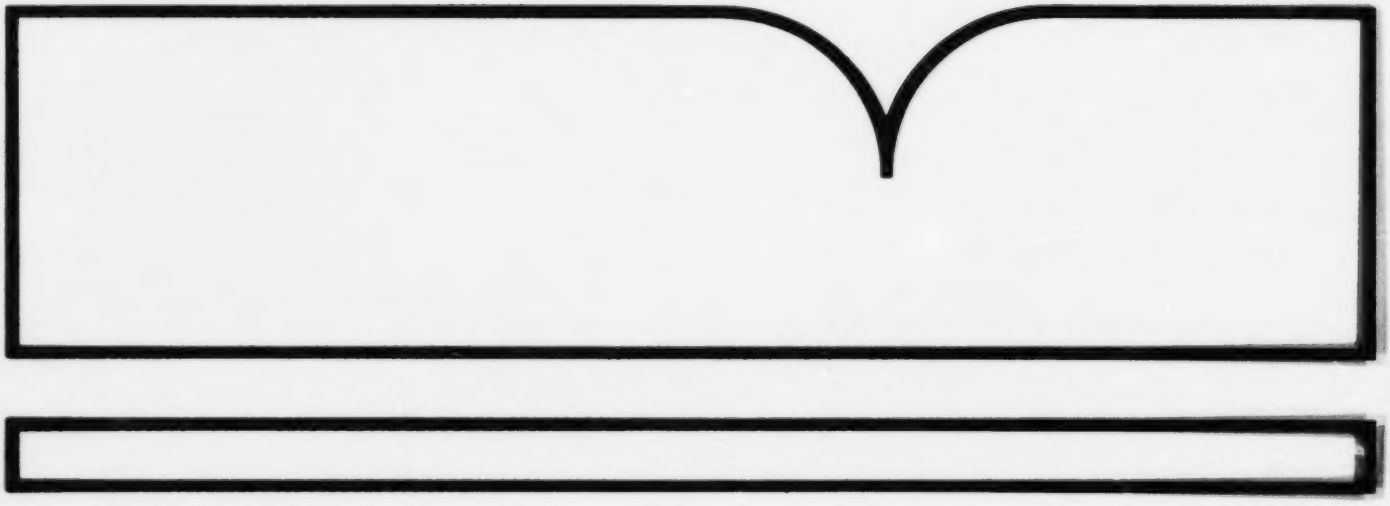

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Design Strategies for Epidemiologic Studies of Environmental Impacts on Health

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16. ABSTRACT

This paper describes epidemiologic designs and methods in studies of health effects of air pollution, whose implications, however, can be extended to the detection of health effects of other environmental exposures. Recent advances in measurement technology for the assessment of both exposure and health responses and rapid developments in the field of biological markers of both exposure and health response offer the opportunity to rectify some past weaknesses or gaps in our ability to draw firm conclusions from environmental epidemiologic studies.

Different design strategies for epidemiologic studies of acute and chronic health effects are discussed with appropriate examples which incorporate the above mentioned technological advances.

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Introduction

The purpose of epidemiologic studies of health effects of air pollution is to quantitatively relate health outcomes in human populations to specific pollutants or mixtures of them in the air. Past studies of the health effects of air pollution can roughly be divided into two broad categories. First, there were those studies carried out in areas and eras of high ambient air pollution levels (very often levels that were more than ten fold the levels currently found in the typical ambient air in the United States) such as the notorious London Fog,[1] Donora,[2] and Meuse Valley (Belgium)[3] episodes, when a relationship was established between those extreme exposures and excess deaths and disease. The attributable risk due to air pollution was high, statistically significant, and did not need very elaborate statistical or epidemiologic design strategies to detect. These studies also led to the passage of clean air legislation in the United Kingdom in 1956, which mandated the reduction of emissions of certain pollutants into the air. This was then followed by a series of epidemiologic studies to evaluate the efficacy of this clean air legislation as a health intervention measure. For example,[4] whereas before the clean air act in the United Kingdom daily symptom diaries of patients with chronic bronchitis revealed a definite relationship between severity of symptoms and measured levels of air pollutants in London, this relationship disappeared after the marked reduction of pollutants (particularly smoke) which followed the clean air act.

However, when such epidemiologic methods are applied to current ambient levels of air pollutants, particularly in the developed world, their power to detect health effects is severely limited by the following circumstances:

(a) The levels of commonly measured pollutants such as SO_2 particulates and lead have been sharply reduced over the past two decades, making health effects more difficult to detect.

(b) The particular health conditions that one expects to be associated with air pollution have undergone changes in incidence, prevalence, and severity for many reasons, not all of which are known, and some related to factors other than air pollution, such as cigarette smoking, occupation, and diet.

(c) The introduction into the environment of new agents, some of which are known to be toxic and others not yet tested, make attribution of risk to any one pollutant more difficult.

Methodology

In order to optimize the efficiency of detection of a health effect of air pollution, appropriate refinements in measurement and specification of what we mean by exposure and what we mean by and how we measure health effects need to be introduced. The magnitude of a health effect can be measured by the relative risk, which is the ratio of the risk for a specific health outcome in a population exposed to a suspected harmful factor, to the risk in a population unexposed to the pollutants under study. Another measure of the risk of exposure is the attributable risk, which is the difference rather than the ratio, between the rate of disease amongst those exposed and the rate of disease amongst those not exposed. Thus the relative risk of dying from lung cancer and cardiovascular diseases among heavy smokers compared to non-smokers is 32.4 and 1.6 respectively, and the attributable risks are 2.2 and 2.6 per thousand per year respectively, signifying that a heavy smoker, in spite of the much higher relative risk of dying of lung cancer, is still more likely to die from the enhanced rate of cardiovascular diseases. With present relatively low levels of ambient air pollution one would expect relative risks in many cases to be so low that epidemiologists would consider most standard approaches inadequate to detect them. However even with very low relative risks, considering the fact that the exposed population (those at risk) could consist of many millions of individuals, one could conceivably be dealing with a major public health problem which is likely to affect many more people than exposures in smaller populations that have relative risks orders of magnitude greater. For example, there are currently approximately 10 million people with chronic obstructive pulmonary disease (COPD) in the United States. Even if only a small portion of these cases are caused or exacerbated by air pollution, we are still talking about sufficiently large numbers of people affected for the health consequences to be of great public health concern. It is this fact that needs to be taken into consideration for the design of future epidemiologic studies.

Before discussing specific design strategies to achieve the above described goals I would like to outline some of the recent technological advances in measuring both exposure and health effects.

Assessing Human Exposure for Epidemiologic Studies

There are many types of questions about health effects of air pollutants that can be addressed by epidemiologic studies.

It is a truism of scientific research that one must ask good questions to get good answers. The nature of the question to be answered will naturally determine the type of exposure assessments to be collected as well as the nature and extent of health effects to be considered.

The major factor that determines the degree and refinement in assessment of exposure is the extent to which we can accurately classify the study subjects by extent and type of exposure to pollutants. Exposure misclassification--imprecise categorization of a person as exposed or non-exposed--is one of the major factors that can cause a failure to detect a real health effect. Let us consider the following hypothetical example. Assume that exposure to 100 units of nitrogen dioxide produces a health effect Z and we compare two communities X and Y. Community X is a rural community where outdoor levels of air pollution rarely exceed 50 units and Community Y an urban one where outdoor levels often exceed 100 units. The rural community turns out to have 3 times the prevalence of the disease Z observed in the urban community. If this were all the information that we were to use for the assessment of health effects we could make the following two possible conclusions: either there is no association between exposures to NO_2 and disease Z or we could even conclude that exposure to nitrogen dioxide protects us from disease Z. But perhaps we are measuring NO_2 in the wrong place. If for example we find out that 80% of our rural study subjects and only 10% of our urban study subjects had at least one gas appliance in their homes, and such appliances cause an average indoor exposure of 300 units of nitrogen dioxide, we will immediately realize that our earlier practice of assigning exposure categories on the basis of outdoor ambient NO_2 levels results in invalid exposure assessment, in this case not only producing the washing out of an effect when there really is one but actually showing a benefit to health.

Spacial aerometric monitoring of air pollution levels in various outdoor sites in the areas inhabited by the populations under study has been and still is a commonly used estimator for doses of pollutants to those populations. Studies in toxicology and molecular epidemiology suggest that exposure assessment needs much greater refinement. At the recent meeting of the Air Pollution Epidemiology Committee of the National Academy of Sciences, we made the following suggestions regarding the use of the term exposure: "'Exposure' commonly refers to concentrations of pollutants measured in the environment. As to dose itself, two distinctions can be made: 'internal dose' is the amount of substance or its metabolites in the body tissues, and 'biologically effective dose' is the amount that interacts with the particular target tissue or its surrogate."[5,6]

Which of the above assessments of exposure are used in epidemiologic studies depends on the specific question to be answered and on the feasibility of obtaining the ideal exposure data for that study. More often than not compromises have to be made: if monitoring personal exposure is not feasible; one might integrate data obtained from outdoor aerometric stations and indoor microenvironmental measurements according to time spent by individuals in those locations in order to obtain total exposures. The accuracy and reliability of such data depends on the type of pollutant measured and the geographical, architectural and emission source characteristics in the areas of study.

There have been major advances in monitoring technology which provide epidemiologists with the means to select those exposure assessment methods that are most suitable for their study design.

One need no longer rely on one or a handful of outdoor air pollution monitoring stations to assess the average exposure of entire populations.[7,8,9] We now know that these measures of outdoor exposure are often invalid. We also know that people spend 80% or more of their time indoors and that the concentration of many pollutants can differ greatly between these two locations.[10,11] Instrumentation including passive monitors has been developed to enable us to conduct intensive monitoring both indoors and outdoors to represent the exposure of populations and individuals more closely. For many pollutants such as nitrogen dioxide, respirable particulates, and carbon monoxide personal monitors have been developed that can be worn by individual study subjects to represent their exposure.

Some recent work monitoring both indoor and outdoor environments using these techniques has demonstrated two remarkable facts. For some regulated pollutants indoor levels have been found in some cases to exceed outdoor levels by orders of magnitude. Within the indoor environment, these pollution levels can vary extraordinarily from room to room and vertically within some rooms, particularly in those where the source is located.[11,12]

The following two important facts should be kept in mind when exposure assessments are made:

(1) Exposures to one or several pollutants measured usually do not comprise all the exposures undergone by the study population that should be considered capable of causing health effects.

(2) Those substances or pollutants are very often surrogates for known or unknown toxic substance, such as for example, T.S.P. (total suspended particulates) or respirable particulates whose sizes and shapes and chemical composition vary widely. The toxic characteristics of the surrogate pollutants need to be identified as much as possible in order to prevent misclassifying exposure to the true agent likely to be associated with the disease outcome.

In summary, greatly improved and readily available monitoring technology together with the greater understanding of spatial dispersion of pollutants once emitted both indoors and outdoors is an important tool in the hands of epidemiologists who use it properly.

Health Effects

There are many health effects plausibly attributed to air pollutants that should be studied; some of these will be discussed in this section. The purpose of this discussion is to raise some of the common issues and problems in the measurement of health effects to be incorporated into epidemiologic studies.

Clinical, animal, and epidemiological studies have shown that the impact of air pollutants is mainly on the respiratory system. A variety of health effects on other organs or systems such as reproductive outcomes and neurological damage have also been demonstrated or are plausible. For the purpose of illustration, we will focus on a number of respiratory health outcomes requiring a variety of research design strategies and methodologies .

Health effects of environmental agents are traditionally divided into two broad categories, acute and chronic. The distinctness and independence of these two types of health responses is not at all clear cut.

Acute health effects are defined as those of relatively short duration ranging from minutes to a few days, such as for example an asthmatic attack. Chronic health effects are those of extended duration, usually over a number of years, such as chronic bronchitis or emphysema. The lack of a clear cut distinction between these two categories mentioned above arises from the fact that the causation and mechanism of progression of most respiratory diseases is poorly understood; in particular, the relationship of acute events to the progression of chronic disease. Chronic effects are usually assumed to be associated with long term exposures as for example, lung cancer and lifelong cigarette smoking history. Acute effects on the other

hand could result from short term exposures as for example, an asthmatic attack immediately following an exposure to specific aeroallergens, or from extended cumulative exposures over longer periods of time which resulted in chronic conditions. Such chronic conditions in turn could result in greater sensitivity and exhibit acute symptoms on exposure to environmental agents (as for example, acute episodes of coughing in patients with lung cancer).

Acute Health Effects

To investigate acute health effects, epidemiologists generally relate exposures preceeding the outcome by periods of times ranging from a few hours to a few days. There are many confounding factors to consider. Confounding factors are factors that are correlated, fortuitously or otherwise, both with the exposure to the agent being studied and the health outcome. An example would be another pollutant whose concentration in ambient air is correlated with the pollutant under study, and which has its own effect on health. The separate effect of these confounders is very difficult to assess, resulting in a wide range of apparent effects attributed to the pollutant under investigation. This has resulted in widely varying and conflicting conclusions derived from many studies of acute health effects of air pollution.[13-19]

Chronic health effects are usually related to cumulative long term exposures. These exposures are very difficult to assess accurately and reliably and their effects on chronic diseases are also very often difficult to separate out from the effects of confounders. Examples of possible confounders in chronic health effects studies are cigarette smoking, and employment in industries associated with increased risk of respiratory illness. Another general difficulty one faces in the study of chronic health effects is that in spite of the fact that the disease manifests itself after decades of exposure, there are very few early markers to identify early stages of disease. This fact not only prevents us from instigating early public health prevention measures before the disease becomes irreversible, it also makes it much more difficult to assess the cumulative exposures to pollutants that trigger the onset of disease.

The types of data that are used to assess health effects whether acute or chronic are:

(1) clinical diagnoses of disease

(2) Data that reflect clinical diagnosis but are not detected clinically, (called subclinical): early markers such as reported symptoms, biologic or physiologic measurements, or morphologic assessements.

The most common acute respiratory effects other than mortality from respiratory diseases that have been studied are increased attacks of asthma, and increases in respiratory infections and symptoms. Asthma is a condition characterized by intermittent obstruction of airflow which can be triggered by allergens and/or various chemicals like toluene di-isocyarate or sulfur dioxide. The obstruction can often be detected by abnormalities in lung function, FEV_1 or peak expiratory flow rate or forced vital capacity while the patient is symptom free. Such transient changes in response to short term exposures have also been shown in a proportion of normal subjects.

Most epidemiologic studies of Air Pollution and Asthma have focused on the question of whether air pollution triggers asthmatic attacks or related symptoms. Recent development in monitoring techniques, particularly personal monitors for estimation of short term exposures, and the availability of portable Spirometers and inexpensive peak flow meters for the frequent recording of pulmonary function by study subjects will greatly assist in the sensitivity of the studies.[20] In such a study a high risk or potentially sensitive population (relatively small in number of subjects) can be assembled and followed over time. In such studies each individual will be monitored for total exposure to selected pollutants (including aeroallergens) on a daily basis for a number of months while simultaneously daily asthma symptom rates and lung function measurements will also be obtained. These data can then be analyzed by a variety of strategies, including the recently developed statistical approaches[21] which use each study subject as his or her own control to determine individual sensitivity. As the number of subjects in a study increases, persons with similar dose-response patterns could be grouped, so that acute effects on the heterogeneous population of asthmatics of a variety of air pollutants can be evaluated.

Such studies in which frequent and extensive measurements of both the exposure and the effect variables are carried out will rarely, because of prohibitive costs, have a large study population. On the other hand, because of the better measurements, they could provide more valid data on health effects, even though the smaller size of the study population may limit the extent to which these results can be extrapolated to the general population. Thus trade-off between costly studies on large populations and validity and reliability of measurements might be considered.

Temporary decreases in pulmonary function in sensitive individuals including asthmatics as a result of exposure

to ozone (22,23) and nitrogen dioxide (24,25,26,27,) have been demonstrated in chamber experiments; findings from different laboratories however have been inconsistent. These findings in chamber studies should serve as the basis for the conduct of epidemiologic studies to investigate population sensitivity to these agents under normal living conditions. The increased use of spirometry in epidemiologic studies would both help identify sensitive populations and further elucidate the relationship between exposure and health effects.

Respiratory Infections

Respiratory infections both bacterial (such as most pneumonias and acute bronchitis) and viral (such as most colds, influenzas and sore throats) have often been linked with air pollutants.[28,29,30,31] Links between exposures to NO_2 or ozone and bacterial infections have also been found in animal studies [32,33,34,35] where the susceptibility to infections is lowered by these exposures. Respiratory infections also play an important role in asthma and are suspected of playing some part in the development of chronic obstructive pulmonary disease. The links between such exposures and the development of infectious diseases can be validated in epidemiologic studies in which personal exposures to NO_2 are related to serological measurements for the assessment of respiratory infections.

Chronic Health Effects

The chronic health effects of air pollution of greatest concern are chronic obstructive pulmonary disease (COPD), decreased growth of lung function in children, and accelerated decrease in pulmonary function with age in adults. Due to difficulties in diagnosis and gaps in understanding the natural history, COPD is often defined operationally--using physiologic markers-- rather than pathologically. For example, COPD is considered to be present when FEV_1 (forced expiratory volume at one second) is less than 65% of the predicted value (adjusted for age, height, weight, race and sex) and FEV_1:FVC (ratio of forced expiratory volume at one second to forced vital capacity) ratio is less than 65% of the predicted value. Air flow limitation which is used to diagnose the COPD syndrome is also a better predictor of long term survival than disease symptoms such as cough or sputum production. Lower rates of increase with age in lung function in children are thought to result in greater susceptibility to COPD. Acceleration of the rate of decrease in FEV_1 in adults increases the risk of COPD. (Lung function in children usually increases with age at a predictable rate until the late teens when it reaches a plateau; after that, during the third decade, it decreases with age at a constant

predictable rate.) There is some evidence[36,37] that both of the changes in pulmonary function, described above, can be brought about by exposure to air pollutants. The extent to which air pollutants interact with each other and other factors both host and environmental to produce changes both transitory and/or permanent in pulmonary function, and their subsequent contributions to the various disease entities that comprise COPD is yet unknown.

The incorporation of physiological markers of chronic health effects, such as the various measurements of pulmonary function, into prospective epidemiologic studies is expected to contribute greatly to the understanding of the natural history of COPD and the contribution of environmental exposures to its inception and progression.

In most populations the relative risks for diseases associated with air pollution are expected to be relatively low (1.1-1.5) and therefore very difficult to detect in conventional epidemiologic studies. Within the general population there is a range of susceptibilities to air pollutants: for example, subjects with pre-existing conditions such as COPD or asthma, the aged and the very young, are considered to be particularly sensitive. In addition, there is evidence that a proportion of healthy subjects may be susceptible to certain pollutants. Descriptive epidemiologic studies need to be carried out to identify susceptible groups and their distribution in the population. Once such susceptible groups are identified, they might be selected for study in specific epidemiologic investigations. Their use very often can increase the statistical power of a study to detect health effects in a population of limited size. Characterization of both extent of exposure and disease rates in different populations being compared can help to avoid studies in populations whose exposure or disease rate does not show sufficient variation for study.

Epidemiologic studies that are likely to provide the strongest scientific basis for causal inference between exposure to air pollution and health outcome are prospective longitudinal cohort studies. In such studies exposure and health effect are obtained for all members of the cohort thus reducing both random and non-random errors. Such studies are usually very expensive compared to ecologic studies in which aggregate measures for both exposure and/or health effects are used. In addition, for chronic health effects such studies take too long a time for public health intervention. Various design strategies can be used to reduce either the cost of these studies and/or their duration. For example, the"nested case-control" method can reduce the cost of obtaining valid results. The study population in such an investigation is followed prospectively,

the health outcome (such as occurrence of disease) is ascertained for the entire cohort but some (usually more difficult or expensive) measures of exposure are obtained only for a fraction of that cohort. For example blood samples that might provide biological markers of exposure could be stored for the entire population but analyzed only for the cases who succumb to diseases of interest and an appropriate number of matched controls.

The best types of studies for inferring causality are intervention studies such as are conducted in randomized clinical trials. Randomized clinical trials of the effects of air pollution are unethical, but intervention studies that investigate changes in health effects that accompany or are a consequence of a reduction in ambient air pollution levels can be carried out. Such studies have been conducted in the United Kingdom when the Clean Air Act of 1956 was instituted. In the United States in spite of the marked reduction in certain pollutants as a result of the Environmental Protection Agency's air quality standards no comparable health intervention studies have been performed. Such studies should be carried out whenever changes in levels of air pollutants can be expected.

Summary

Studies of air pollution-health relationships are more difficult than they used to be: levels are lower, disease patterns have changed for a variety of reasons, new pollutants are constantly being introduced into the environment.

Accurate pollution exposure assessments are needed, and new technologies may provide them: examples are personal monitors and portable continuous monitors which may be used both outdoors and indoors where recent studies have shown certain pollutants may occur at higher levels.

The study of health effects usually distinguish between chronic and acute effects, which sometimes amounts to drawing a line where no line belongs. Health effect studies may be made more sensitive by selection of high risk populations, and the use of biological markers to supplement clinical evaluations. Portable, easily used instruments to study pulmonary function provide an example.

Some new epidemiological designs are considered that can achieve good reliability while avoiding excessive cost.

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